## REMARKS

**Status of the Claims**

Claims 1-15 were pending. Claims 1 and 6-15 were withdrawn from consideration pursuant to a Restriction Requirement that has been made FINAL and claims 2-5 were under active examination. Claim 2 has been amended as shown above to make explicit that the sequences of the array are polynucleotide sequences and that the polynucleotide sequence corresponding to accessible regions are isolated using a probe that exhibits altered reactivity with an accessible region as compared to bulk chromatin. See, e.g., page 12, lines 29-30 and page 24, lines 3-5. In addition, claim 2 has been amended as shown above to specify that the polynucleotide sequences are at least 25 nucleotides in length as described on page 42, line 24 of the as-filed specification. Withdrawn claim 1 has been similarly amended. Thus, claims 1-15 are pending and claims 2-5 are under active examination. Rejoinder of the method claims containing all the limitations of the examined claims is requested.

**Priority**

Applicants note that the application was filed with a copy of the PCT. In addition, International Bureau (IB) forwarded a copy to the USPTO on June 3, 2004.

**Drawings**

Applicants submit replacement drawings herewith.

**35 U.S.C. § 112, 1st paragraph, written description**

Claims 2 to 5 were rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not adequately described by the as-filed specification. (Office Action, paragraphs 9-17). In particular, it was alleged that insufficient sequences were disclosed to show possession of the claimed arrays and that the process used to isolate accessible regions fails to describe the claimed arrays. *Id.* In addition, it was asserted that no such nucleotides had been prepared and that the written description requirement cannot be satisfied by showing "obviousness." *Id.*

Applicants traverse the rejection and supporting remarks.

The fundamental factual inquiry in written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. *See, e.g., Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117.

Satisfaction of the written description requirement does not necessitate that the specification set forth the sequence of every single nucleic acid by structure in the specification. See, *Falkner v. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006); *Capon v. Eshhar* 76 USPQ2d. 1078 (Fed. Cir. 2005). Working examples of multiple representative species are also never required to show possession. *Id.* Finally, determining whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. See, e.g., *In re Lange*, 209 USPQ 288 (CCPA 1981).

As a threshold matter, Applicants note that, as disclosed in the Examples, approximately 40,000-50,000 clones corresponding to accessible regions were actually generated. See, page 62, line 29 of the specification.[1] Furthermore, 405 of these clones were further analyzed in a variety of ways. See, Example 2. The written description in this case does not require a listing of the precise sequence of any of the accessible region-containing clones. Rather, all that is required is that the specification evince possession of the polynucleotides forming the claimed arrays. In this case, the specification more than amply meets this requirement in explicit disclosure of a multitude of polynucleotides corresponding to accessible regions.

Applicants were also clearly in possession of arrays comprising nucleic acid sequences corresponding to these demonstrated accessible region sequences. The as-filed specification provides pages of disclosure on how to form an array from the exemplified accessible regions. See, Section "V. Arrays" beginning on page 51. As noted above working examples are never required and, given the ample disclosure regarding array construction, the skilled artisan would have no doubt that Applicants were in possession of the claimed arrays at the time of filing.

[1] SEQ ID NO:1 as cited on page 7 of the Office Action is not the sequence of an accessible region – it is the sequence of a zinc finger protein.

Moreover, contrary to the Examiner's assertion, it is not a reliance on "obviousness" to show that the state art at the time of filing establishes that accessible regions (*e.g.,* isolated as exemplified) could readily be used to form arrays. Rather, as noted above, the written description requirement does not require that the specification reiterate known techniques and, indeed, an applicant should preferably omit what is well known. In the instant case, a myriad sequences corresponding to accessible regions are exemplified and described. Furthermore, it is clear from the specification and numerous references are cited in the "Arrays" section that Applicants' were in possession of arrays comprising these sequences.

Simply put, there is absolutely no requirement that Applicants exemplify all nucleotide sequences falling within the scope of the claims in order to adequately describe the claimed arrays. Rather, the test is whether the specification, read in light of the state of the art, contains sufficient disclosure regarding the claimed arrays to satisfy the written description requirement. In the pending case, thousands of sequences were isolated and hundreds characterized. Furthermore, there is clear description in the specification of how to make and use arrays comprising these sequences corresponding to accessible regions using conventional molecular biology techniques. These facts establish that the specification as filed more than adequately describes and details characteristics of the claimed arrays.

**35 U.S.C. § 112, 1st paragraph, enablement**

Claims 2 to 5 were rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not enabled by the as-filed specification. (Office Action, paragraphs 18-19). U.S. Patent Nos. 6,077,674 and 5,858,671 were cited as allegedly showing unpredictability in making arrays. Applicants traverse the rejection.

As set forth in the seminal case of *In re Marzocchi,* 439 F.2d, 220, 223, 169 USPQ 367, 369 (CCPA 1971), a patent application is presumptively enabled when filed:

> [a]s a matter of Patent Office practice ... a specification .. must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Moreover,

> it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 224, 169 USPQ at 369-370. Indeed, as pointed in the Patent Office's own Training Manual on Enablement (1993, citing *In re Wright,* 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), "the case law makes clear that properly reasoned and supported statements explaining any failure to comply with section 112 are a requirement to support a rejection."

In the instant case, the Examiner has not presented a properly reasoned and supported basis for the rejection. For the reasons presented above with regard to written description, the specification and evidence of record clearly establish that the as-filed specification teaches the skilled artisan how to make and use arrays comprising sequences corresponding to accessible regions. The specification also teaches precisely how to isolate sequences corresponding to accessible regions based on their altered reactivity to a probe of chromatin structure (e.g., pages 13 and 24-39). Moreover, the specification, in view of the state of the art at the time of filing, teaches how to make arrays comprising these sequences corresponding to accessible regions (e.g., pages 51 et seq. and references cited therein) and how to use these arrays for high-throughput screening (e.g., Section VI. Applications beginning on page 55, including for example, identification of binding sites for regulatory proteins, identification of sequence targets, RegDNA chip profiling, chromatin epigenome profiling, etc.). See, also, remarks regarding rejection under 35 U.S.C. § 101 below.

Thus, there is ample disclosure in the as-filed specification to allow the skilled artisan to make and use the claimed arrays. Exemplification is not required to show enablement. Applicants also remind the Office that it is well settled that time-consuming or expensive experimentation is **not** undue if it is routine. (See, *e.g.,* PTO Training Manual on Enablement,

pages 30-31, citing *United States v. Telectronics Inc.,* USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied* 490 U.S. 1046 (1989) holding the disclosure of a single exemplified embodiment and a method to determine other embodiments was enabling, even in the face of evidence that determining additional embodiments might require 6-12 months of effort and cost over $50,000). Thus, in the instant case, Applicants are not required to actually have exemplified an array as claimed – the disclosure is more than ample to allow the skilled artisan to make and the use the claimed arrays without undue experimentation.

In this regard, the references cited by the Examiner do not in any way establish lack of enablement of the claimed arrays. Jones was filed in 1996, at least 6 years before the effective filing date of the instant application. Schleifer was filed in 1999, 3 years before the case at hand. Thus, these references not indicative of the state of the art regarding arrays at the time of filing. Indeed, the references cited by Applicants regarding arrays, including U.S. Patent No. 6,600,031; 6,326,489; 6,548,021 and WO 02/18648 are much more germane to the state of the art of the regarding array construction.

For the reasons set forth herein, any experimentation needed to make and use the claimed arrays is routine in view of the teachings of the specification and the state of the art. Thus, the Office has not provided sufficient evidence supporting non-enablement and, in the absence of necessary relevant evidence contradicting the teachings of the specification and state of the art, the rejection cannot be maintained.

**35 U.S.C. § 101/112**

Claims 2 to 5 were rejected under 35 U.S.C. § 101 and § 112 on the grounds that the claimed invention is not supported by a specific, substantial and credible (or well-established) utility based on the assertion that not all nucleic acids have utility. (Office Action, paragraphs 21-25).

Applicants traverse the rejection and submit that the Examiner is applying an improper standard for compliance with the utility requirement.

In particular, there are three basic utility criteria -- specific, substantial and credible. Alternatively, the presence of a well-established utility is sufficient to meet the utility requirements of 35 U.S.C. § 101/112. Applicants submit that, although they need only satisfy

one of these two alternatives, they have provided both specific, credible and substantial utilities, as well as a well-established utility, for the arrays as claimed.

It is well settled that a utility rejection should not be imposed where there is a well-established utility and/or where there is one credible utility (*see,* M.P.E.P. § 2107, emphasis added):

> If at any time during the examination, **it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility**. ...
>
> (1) If the applicant has asserted that the claimed invention is useful **for any particular practical purpose** (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, **do not impose a rejection based on lack of utility.**
>
> ... An applicant need only provide **one** credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

Thus, if the applicant has asserted that the claimed invention is useful for any particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility is improper. Applicants have complied with these standards.

In the pending case, the application sets forth a number of specific uses for the present invention. Here, the claims are not directed to nucleic acids generally. Rather, they are directed to arrays comprising sequence corresponding to accessible regions. The utility of arrays that can measure binding to sequences corresponding to accessible regions is discussed in detail throughout the as filed specification, for example on pages 55-61. These utilities includes identification of regulatory proteins, identification of DNA-binding proteins, RegDNA chip profiling, chromatin epigenome profiling, toxicity profiling, SNP interrogation, microRNA validation, drug discovery, expression profiling, etc. These utilities are clearly credible (as well as substantial and specific). Moreover, they are well-established utilities.

It appears that the Examiner will not consider a utility for the claimed arrays in the absence of working examples regarding the arrays *per se*. If this were the standard, the concept

of "well known" utility would be meaningless. Applicants submit that they have provided credible, specific and substantial utility, as well as a well-established utility, for the arrays of the present invention.

Based on the foregoing, applicants respectfully submit that the rejections under 35 U.S.C. §101, for lack of utility, should be withdrawn.

**35 U.S.C. § 112, 2nd paragraph**

Claims 2-5 were rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite for reciting "sequences," "accessible regions," and "probe of chromatin structure." (Office Action, paragraphs 26 to 30).

Applicants submit that the foregoing amendment to claim 2 obviates the rejection based on allegedly indefiniteness of whether the array was made up of protein or nucleotide sequences.

Applicants remind the Examiner that the definiteness requirement of 35 U.S.C. § 112, second paragraph is satisfied if it is clear to the skilled artisan what is meant by a particular claim term. *See, e.g., In re Marosi,* 218 USPQ 289 (Fed. Cir. 1983). Further, the definiteness and clarity of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular disclosure; (2) the teachings of the art; and (3) the claim interpretation that would be given by one possessing ordinary skill in the pertinent art at the time the invention was made. *See, e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.,* 220 USPQ 202 (Fed. Cir. 1983). In other words, the terms at issue must be read in context of the application and field of endeavor.

It is clear from the as-filed specification and state of the art that the terms "accessible region" and "probe of chromatin structure" are sufficiently definite. The definitions of "accessible region" and "probe" are found at page 12, line 26 to page 13, line 29 and plainly set forth that accessible regions of cellular chromatin are any regions of chromatin that are not bulk chromatin and that a probe is any enzyme or chemical that has altered reactivity with accessible chromatin as compared to bulk chromatin. See, also, page 24, line 29 to page 25, line 8 of the as-filed specification:

> The accessibility of DNA in chromatin refers to any property that distinguishes a particular region of DNA, in cellular chromatin, from bulk cellular DNA. See, for

example, Wolffe "Chromatin: Structure and Function" 3rd Ed., Academic Press, San Diego, 1998 for a description of cellular chromatin. For example, an accessible sequence (or accessible region) can be one that is not packaged into nucleosomes, or can comprise DNA present in nucleosomal structures that are different from that of bulk nucleosomal DNA (e.g., nucleosomes comprising modified histones). An accessible region includes, but is not limited to, a site in chromatin at which an enzymatic (e.g., DNAseI) or chemical probe reacts, under conditions in which the probe does not react with similar sites in bulk chromatin. Such regions of chromatin can include, for example, a functional group of a nucleotide, in which case probe reaction can generate a modified nucleotide, or a phosphodiester bond between two nucleotides, in which case probe reaction can generate polynucleotide fragments or chromatin fragments.

Therefore, in light of the specification as a whole, the skilled artisan would clearly be apprises as to the metes and bounds of the claims. Accordingly, the rejection cannot be sustained.

**35 U.S.C. § 102(b)**

Claims 2 to 5 were again rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Brennan. (Office Action, paragraphs 35-43). In response to the previous argument that Brennan's polynucleotides do not necessarily correspond to accessible regions of the cellular chromatin, it was asserted that the claims do not recite "typical nucleosome structure;" that the inclusion of "variants" is encompassed by the claims and that the recitation "altered reactivity to a probe of chromatin structure" was unclear.

Applicants again traverse the rejection and supporting remarks.

To reiterate, the pending claims are drawn to arrays that consist only of sequences corresponding to accessible regions of cellular chromatin, wherein accessible regions are isolated based on altered reactivity to a probe of chromatin structure (as compared to reactivity of bulk chromatin to that same probe). In addition, the claims require the sequences on the array to be at least 25 nucleotides in length.

As acknowledged, Brennan's sequences are all 10-mers, which are significantly shorter than the claimed at least 25-mers. On this basis alone, the rejection cannot stand.

Furthermore, while the polynucleotides on the claimed arrays are naked DNA in that there is no nucleosome structure, they are distinct in structure from Brennan's random 10-mers

by corresponding to accessible regions based on how they were isolated. Every single sequence on the claimed array corresponds to an accessible region of cellular chromatin. Brennan's arrays are random 10-mers and, as such, do not consist of sequences corresponding to accessible regions of chromatin. Furthermore, variants that do not correspond to accessible regions are not encompassed by the claims.

Thus, the continued insistence by the Examiner that the claims encompass virtually any polynucleotide sequence is in unfounded. In the instant case, an array of sequences consisting of sequence corresponding to accessible regions, which are isolated based on altered reactivity to a probe of chromatin structure, is structurally distinguishable from Brennan's arrays. Whereas the claimed arrays include only sequences corresponding to accessible regions, Brennan's arrays are not necessarily sequences corresponding to accessible regions and, indeed, because they are random, will have sequences corresponding to non-accessible regions.

Therefore, because Brennan does not disclose all the elements of the claims and because the evidence or record clearly establishes that the recited process steps impart structural limitations that distinguish the claims from the arrays of the cited reference, Brennan cannot anticipate any of the pending claims and withdrawal of the rejection is in order.

## CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that all of the pending claims are in condition for allowance and request early notification to that effect.

Should the Examiner have any further questions, Applicants request that the undersigned be contacted at (650) 493-3400.

Respectfully submitted,

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